

SSCP genotyping

SSCP genotyping was performed using polymerase chain reaction (PCR) with exon 2 internal primers, amplifying a 120-base pair portion of the PBR, and subsequent capillary electrophoresis on an ABI310 automated sequeencer²⁵ with modifications. These were the inclusion of a second different reverse primer (GTT GTG CAG ACA GTA AAC CTC CTT C) to increase the number of alleles detectable with SSCP. Both primer pairs together amplified 17/24 (thus 74%) of the PBR that was identified by sequencing in the experimental fish. Isolated sequences cloned into plasmids were subjected to SSCP in order to standardize the fluorescent signals with sequence information. In three cases, complete PBR residues that differed only in 2–4 amino acids cannot be resolved by SSCP, such that our method underestimated the true MHC class-IIb diversity. In all cases, SSCP signals obtained from PCR of plasmids were also present in genotypes based on fish DNA.

Microsatellite genotyping, heterozygosity and relatedness

All fish of the first experimental block were genotyped for seven polymorphic microsatellites (GenBank accession numbers: AJ010352, -54, -55, -57, -58, -60; ref. 26), representing a total of 72 alleles. Individual heterozygosity was calculated as the number of different alleles per microsatellite locus, and as mean d^2 taking the length difference of alleles into account²⁷. We calculated a correlation between allele number of MHC class-IIb loci and individual heterozygosity. Relatedness coefficients R (ref. 28) were calculated for all pairs of fish using a program called Relatedness 5.0 (K. F. Goodnight, available from <http://gsoft.smu.edu/gsoft.html>). R coefficients were tested for correlation with female mating behaviour using the time difference of females among preferred/unpreferred male as variable for the female preference.

Permutation procedure

The risk that females will choose an MHC-identical male, or a male with fewer alleles, when mating completely at random was assessed in a permutation procedure. We combined 46 male and 46 female genotypes from Schöhsee 100 times at random, each time counting genotypic similarity and difference in allele number.

Sexual selection experiments

Adult three-spined sticklebacks were seine-netted from an interconnected natural system of large lakes near Plön, Germany, in spring. A bit of a dorsal spine of each fish was cut for MHC class-IIb and microsatellite genotyping (see above). Thereafter fish were housed in individual tanks (10 litres, continuous exchange of 1 litre per hour, 18°C, 18 h of light). Males (every second tank) were offered artificial nesting material. Only bright red males with completed nests were used for experiments.

Gravid females were tested in a flow channel²². In the test compartment (25 × 20 cm long, 10 cm water level) each female was offered the choice between the two sides of the current (1.4 cm s⁻¹), which was video-recorded from above. The inlet compartment, which was separated upstream by a net from the test compartment, was divided laterally into halves. A peristaltic precision pump (ISMATEC MV, 100 W, 50 Hz) supplied water (2 × 65 ml min⁻¹) taken from the tanks of each of two males with defined MHC II properties through silicon tubes to the halves of the inlet compartment in the sequence: 2 min neutral water, 5 min 'male' water, 2 min neutral water, 5 min 'male' water after switching sides. The bottles with the stimulus water had been coded by a third person. Each of 50 females was tested only once. Of the 57 males in both experiments, there were three combinations in the disassortative experiment which were tested twice.

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Illusory perceptions of space and time preserve cross-saccadic perceptual continuity

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When voluntary saccadic eye movements are made to a silently ticking clock, observers sometimes think that the second hand takes longer than normal to move to its next position¹. For a short period, the clock appears to have stopped (chronostasis). Here we show that the illusion occurs because the brain extends the percept of the saccadic target backwards in time to just before the onset of the saccade. This occurs every time we move the eyes but it is only perceived when an external time reference alerts us to the phenomenon. The illusion does not seem to depend on the shift of spatial attention that accompanies the saccade. However, if the target is moved unpredictably during the saccade, breaking perception of the target's spatial continuity, then the illusion disappears. We suggest that temporal extension of the target's percept is one of the mechanisms that 'fill in' the perceptual 'gap' during saccadic suppression. The effect is critically linked to perceptual mechanisms that identify a target's spatial stability.

Although most observers have experienced the 'stopped clock' illusion, previous psychophysical experiments that have tested when subjects perceive the time of transient external events relative to saccadic eye movements have yielded contradictory results^{2,3}. A

possible reason for this is that the saccade itself causes changes in temporal perception at around the time of eye movement. We tested whether the perceived duration of chronostasis is affected by the duration of the saccade. Subjects made saccades of either 22° or 55° degrees (lasting on average 72 and 139 ms, respectively) to a numerical counter. The movement of the eyes was used to start the counter (which proceeded at one increment per second) with the exception that the duration of the first number could be varied between 400 and 1,600 ms. Subjects had to state whether the time that they had seen the first digit was more or less than that for the subsequent digits (a constant 1 s). Figure 1 shows that subjects thought they had seen the initial digit for 1 s when their gaze had been on the target for only 880 ms (22° saccade) or 811 ms (55° saccade). Control trials in which the same temporal judgement was made either without moving the eyes, or if the target rather than the eye saccaded into the visual field, gave significantly different values that were very close to the correct value of 1 s. There was an almost exact agreement between the extra time taken for the eyes to move over the longer distance (139 – 72 = 67 ms) and the difference in the time intervals that subjects matched to 1 s (880 – 811 = 69 ms), suggesting that the illusion of chronostasis is linked to the time taken to move the eyes. In fact, subjects seemed to extend the time that they thought they had seen the first target back in time to approximately 50 ms before the start of the eye movement.

Although subjects reported no awareness of the counter changing during their saccades, it is possible that they were able to use this digit shift as a cue to initiate time judgements. This would invalidate the matched times we calculated (measured from the moment the eyes actually reached the counter). However, a control experiment in which the counter was triggered either very early or very late during a large (55°) saccade showed no difference in the duration of chronostasis, despite modifying the period that the digit was actually on screen by 85 ms.

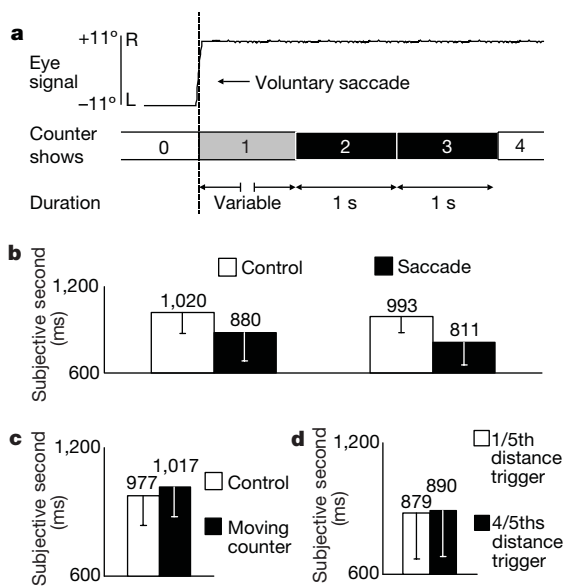


Figure 1 Results for experiment 1. Error bars show standard deviations. **a**, Schematic of experimental method. **b**, Mean time (ms) matched to 1 s for two conditions involving saccades of 55° and 22° (right and left pf figure, respectively) and two control conditions (without saccades) at matched eccentricities. Chronostasis occurs in both experimental conditions compared with controls (55°: $t_{29} = 9.612$, $P < 0.001$; 22°: $t_{29} = 5.608$, $P < 0.001$) and increases linearly in one-to-one correspondence with saccade duration ($t_{29} = 2.553$, $P < 0.05$). **c**, Results for a control experiment where the counter moves to the point of fixation. Chronostasis is not obtained. **d**, Results for a comparison between the standard interval from saccadic onset to counter change and a much longer interval. The duration of chronostasis is unaffected.

The tight coupling of the duration of chronostasis to the duration of the saccade suggests that the effect may be linked to the perceptual gap caused by saccadic suppression and retinal blur that occurs when we move the eyes^{3,4}. However, it is possible that the illusion of chronostasis is not tightly coupled to movement of the eyes per se, but occurs because subjects also shift the locus of their visual attention at around the time their eyes move⁵. This attention shift may act as the reference point to which the target is predated. To test this, subjects were asked either to make the usual saccade to the target or first to shift their attention to the target and then move their eyes. Figure 2a shows that the illusion of chronostasis persisted with a similar magnitude when subjects shifted their attention before moving their eyes. Control trials intermixed with the eye movement trials verified that subjects were successful in shifting the locus of their visual attention⁶. They fixated on a central cross and had to saccade to a target appearing on the right or left of the screen. If they had been told to shift their attention to the correct side before the target appeared, their reaction time was faster than if they had been incorrectly cued (Fig. 2b).

Although chronostasis is linked to voluntary saccades, the coupling is not obligatory—there is at least one condition under which the illusion is not experienced. We designed a third experiment in which the positional stability of the target counter was systematically broken. Subjects made a saccade to the target, but in some trials the computer displaced the target by up to 9° during the time the eyes were moving. Under such conditions, subjects sometimes fail to notice the shift and make an unusually large corrective saccade to fixate the target^{7,8}. Trials were divided into three types: (1) those in which the counter remained stationary throughout; (2) those in which it was moved but the movement was not perceived by the subject; and (3) trials in which target movement was perceived by the subjects. Figure 3 shows the results of this experiment. When there was no target motion, subjects experienced the usual illusion of chronostasis when they made a saccade compared with a control condition with no movement of the eyes. However, if the target was moved and subjects noticed the movement, then no effect was found relative to control. If the shift

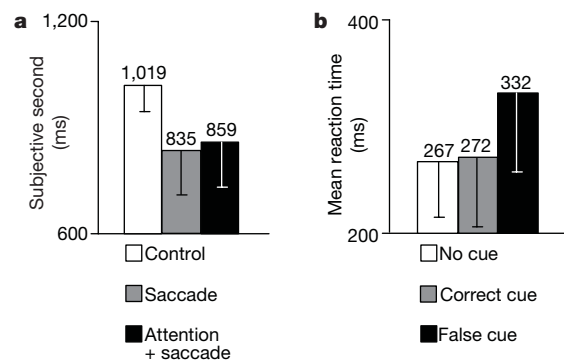


Figure 2 Results for experiment 2. Error bars show standard deviations. **a**, Mean time (ms) matched to 1 s for two conditions involving saccades with/without early, deliberate reorienting of attention, and a control condition. Shifts of attention cannot account for chronostasis because covertly shifting attention early on does not influence the size of the effect. The low value for subjective seconds appears to differ from the results related to saccade duration of experiment 1 (Fig. 1) for a shorter (12°) saccade. However, intersubject variability is high for this task; when data for only those 9 subjects who participated in both studies is considered, the results continue to support a linear effect size scaling with saccade duration. **b**, Mean reaction time (ms) for a two-choice saccade task with no cue to direct attention, a correct cue, or an incorrect cue. Subjects succeeded in reorienting attention, as confirmed by the significantly lower reaction time for the correct cue and no attention conditions relative to the incorrect cue condition (correct cue: $t_{11} = 4.108$, $P < 0.01$; no attention: $t_{11} = 5.367$, $P < 0.001$). Error data (not shown) displayed a similar pattern.

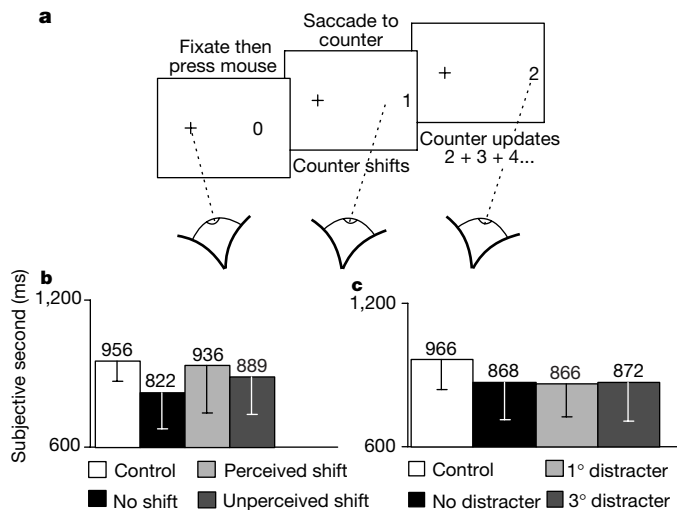


Figure 3 Results for experiments 3 and 4. Error bars show standard deviations. **a**, Schematic of a shift trial (experiment 4). **b**, Mean time (ms) matched to 1 s for four conditions: standard saccade (20°); saccade with detected counter displacement ($\pm 0-9^\circ$); saccade with undetected counter displacement ($\pm 0-9^\circ$); and control. Chronostasis (standard saccade $t_{21} = 4.283$, Bonferroni $P < 0.01$) is eliminated when saccade target stability is noticeably violated and moderated when such a violation goes

unnoticed. **c**, Mean time matched to 1 s (ms) for four conditions: standard saccade (20°); saccade with appearance of a distracter 1° from the target; saccade with appearance of a distracter 3° from the target; and control. Chronostasis is obtained regardless of the distracter (standard: $t = 3.50$, Bonferroni $P < 0.05$; 1° distracter: $t = 3.220$, Bonferroni $P = 0.063$; 3° distracter: $t = 3.724$, Bonferroni $P < 0.05$).

was not perceived, the estimates of the subjects fell somewhere between the control value and the full illusory effect. The effect of moving the target was not due to nonspecific distraction caused by the shift. The full illusion was again obtained in our final experiment, in which distracting stimuli appeared randomly 1° or 3° to the side of the target during the time the eyes were moving, and remained on the screen thereafter (Fig. 3).

Thus, backwards extension of the perception of the target only occurs when subjects perceive that the saccadic target was stationary during the period of extension. We suggest that this link between space and time occurs because of the following. When the saccade shifts the eyes from one stationary viewpoint to another, vision is degraded and it is not possible to say with certainty whether there are any changes in the position of objects during movement. However, if the saccadic target is fixated accurately at the end of the saccade, subjects can assume that it occupied approximately the same place throughout the eye movement (object constancy). Such an assumption may fulfil various functions, having already been proposed in recent theories relating to the problem of space constancy⁹⁻¹¹. As there is no other competing percept (because vision is blurred during the saccade), the assumption of a constant target position is linked to an extended temporal perception of the object as seen at the end of the saccade. If the target jumps, then object constancy is broken, and chronostasis fails to occur. Conscious awareness of a target jump may be linked to the assumption of object constancy, but is unlikely to mirror it precisely. This may explain the partial (nonsignificant) effect for targets that shift without the subject becoming aware of this change.

Perception of the target, rather than being extended back to the time of saccadic onset, predates this by up to 120 ms. Although predating of the target's postsaccadic state to a specific pre-motor event (such as the efferent command) is one possibility, it is notable that the processes underlying both saccadic suppression and space constancy are active over a time period extending beyond the saccade itself⁴. Our obtained constant values are similar to the value of 80 ms obtained for presaccadic shifts in neuron receptive fields within the lateral intraparietal area of monkeys¹². They also fit well with human psychophysical data on presaccadic compression of space (the systematic mislocalization of targets flashed around the time of a saccade) and saccadic suppression, which both precede

saccadic onset by 50 ms or more^{13,14}. It therefore seems probable that presaccadic mechanisms will provide an explanation for the time course of chronostasis.

These data support ideas of conscious experience as an ongoing, often post hoc reconstruction emerging from multiple cognitive systems¹⁵⁻²¹. Our suggestions relating to assumed continuity of target appearance fit well with ideas about object files in the visual attention literature^{22,23}. Here, features of a visual object (colour, form, location, and so on) are bound into a single perceptual unit (the object file) that links representational codes established across diverse cortical regions. We suggest that cross-saccadic perceptual continuity, as described here, may represent a specific case of a more general class of phenomena relating to the continuity of perception across shifting states of sensory input. □

Methods

Experimental design

Subjects sat before a 14-inch colour monitor (60 Hz refresh), with their chin supported. Eye movements were recorded using electro-oculography or with an infrared eye tracker (Microguide 1000 spectacles), and sampled at 200 Hz. Stimuli were black on a white background or vice versa, subtending approximately 0.5°. The experiments were controlled by a personal computer interfaced with a 12-bit A/D card (National Instruments DAQ 1200). Counter change was triggered when the eyes had travelled one fifth of the distance to target. We calculated saccade start/end points automatically using a velocity criterion. Repeated measures designs were used throughout, with condition order counterbalanced. We calculated n for each experiment following a power analysis of initial data sets. Later experiments replicate experiment 1 unless stated otherwise.

Experiment 1

Thirty subjects (18 male, mean age 28.2, standard deviation, s.d. 7.4) completed four conditions: saccades of 55° and 22° and two matched control conditions. In the two saccade conditions, subjects fixated on a cross on one side of the screen, initiated the trial with the depression of a key, and then made a voluntary saccade to a target '0' on the other side of the screen. Eye movement triggered a change of digit to a '1', which remained on the screen for 400-1,600 ms; subsequent digits (2, 3) remained on the screen for 1 s each, culminating in the appearance of a '4'. Subjects indicated whether the time that they saw the '1' for was longer or shorter than that for the subsequent digits. Trials where the first saccade recorded did not exceed 90% of the total distance to target were excluded and immediately repeated. In control trials, subjects fixated a '0' at equivalent eccentricity that changed to become the judged digit (1) 500 ms after the subject's key press. The computer controlled the duration of the first digit by a modified binary search (MOBS)²⁴ procedure that homed in on a single, matched estimate (low boundary 400 ms, high boundary 1,600 ms, initial presentation random 800-1,200 ms, five reversals to terminate). Four estimates

were obtained per condition, then corrected post hoc to match the time that the '1' was on screen after target foveation.

Ten subjects (9 male, mean age 30.5, s.d. 7.8) completed a control experiment. They estimated the duration of the first digit when a counter moved 24° to the point of fixation in 100 ms (six screen refreshes), compared with the usual stationary control. A further control experiment ($n = 10$, 9 male, mean age 31.4, s.d. 7.6) varied the time from saccade onset to the initial counter change by triggering this change either one fifth or four fifths of the way into a 55° saccade (randomly within the same block; separate self-terminating MOBS).

Experiment 2

The data of 12 subjects was included in experiment 2 (10 male, mean age 32.8, s.d. 9.3). In addition to a control, subjects completed two conditions requiring 12° saccades to a counter (as experiment 1) with or without deliberate, prior covert shifting of attention. Every other trial was a reaction time task in which subjects fixated the central target and then made a speeded 12° saccade to the appearance of a target '0' to the left or right. An uninformative cue (an arrow pointing to the left or right near fixation) directed attention before the appearance of the '0' in attention-shift blocks.

Experiment 3

Twenty-two subjects performed experiment 3 (16 male, mean age 30.8, s.d. 7.4). We tested three conditions: a 20° saccade to a stationary counter; a 20° saccade in which the counter shifted ± 0 –9° synchronous with triggering of counter onset; and a control. All eye movement data were obtained within a single block type in which subjects made the standard timing judgment and also indicated whether the counter had moved during the saccade. Presentation was controlled by three randomly interleaved (equally probable) self-terminating MOBS. The first of these controlled target time intervals for the stationary counter trials (as in experiment 1), the latter two controlled the size of the target shift in a hypo- or hypermetric direction (0–9°) according to whether the movement was perceived. This ensured that most of the shift trials were close to the subject's point of shift perception, whether perceived or not. For shift trials, the target time interval was randomly generated in the range 400–1,600 ms. Trials were divided between perceived and unperceived shift conditions post hoc. For all conditions, matched time estimates were generated using logistic regression. Subjects initially completed four experimental blocks and four short control blocks, with a single additional block completed where fitted logistic regression lines exceeded $P = 0.05$.

Experiment 4

Ten subjects participated in experiment 4 (7 male, mean age 29.4, s.d. 7.5). We compared four conditions: a 20° saccade to a stationary counter; an identical saccade with a random, lower-case alphabetic character appearing 1° from the counter (hypo- or hypermetrically) at trigger time; a saccade with the character appearing 3° from the counter; and a control. Data for the first three conditions was obtained within a single block type, using three randomly interleaved and self-terminating MOBS.

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Haemoglobin C protects against clinical *Plasmodium falciparum* malaria

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Haemoglobin C (HbC; $\beta 6\text{Glu} \rightarrow \text{Lys}$) is common in malarious areas of West Africa, especially in Burkina Faso^{1,2}. Conclusive evidence exists on the protective role against severe malaria of haemoglobin S (HbS; $\beta 6\text{Glu} \rightarrow \text{Val}$) heterozygosity³, whereas conflicting results for the HbC trait have been reported^{4–10} and no epidemiological data exist on the possible role of the HbCC genotype. *In vitro* studies suggested that HbCC erythrocytes fail to support the growth of *P. falciparum*^{11,12} but HbC homozygotes with high *P. falciparum* parasitaemias have been observed¹⁰. Here we show, in a large case–control study performed in Burkina Faso on 4,348 Mossi subjects, that HbC is associated with a 29% reduction in risk of clinical malaria in HbAC heterozygotes ($P = 0.0008$) and of 93% in HbCC homozygotes ($P = 0.0011$). These findings, together with the limited pathology of HbAC and HbCC¹³ compared to the severely disadvantaged HbSS and HbSC genotypes and the low β^S gene frequency in the geographic epicentre of $\beta^{\text{C}1,2,14}$, support the hypothesis that, in the long term and in the absence of malaria control, HbC would replace HbS in central West Africa.

Since hominization the human genome has been under selective pressures for resistance to infectious diseases. For example, West African populations are able to escape the infection altogether, with complete protection from *Plasmodium vivax* achieved through the fixation of a Duffy silent allele (fy)¹⁵. In other cases, polymorphic